IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF TEXAS
(HOUSTON DIVISION)

GAYATHRI MURTHY, Plaintiff,	§ § §	
v.	§	CASE #: 4:11-cv-00105-KPE
ABBOTT LABORATORIES, Defendant.	§ § §	

PLAINTIFF'S RESPONSE IN OPPOSITION TO DEFENDANT'S MOTION TO EXCLUDE CAUSATION TESTIMONY

Respectfully submitted,

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Q. Okay. So if they're in the warnings, there's reasonable evidence of a causal association, true?

A. Yes, that's the standard.

Q. Serious infections?

A. Yes.

Q. Lymphoma?

A. Yes.[1]

This sworn testimony by Abbott's own expert witness, Dr. David Feigal, an epidemiologist, physician, former FDA official, and purported FDA regulatory expert, was given on May 3, 2013 in the case of *In Re Humira Litigation: Delores Tietz and Milton Tietz v. Abbott Laboratories*, Case No. L002715, in the Circuit Court of Cook County, Illinois. It is a **judicial admission** that there is reasonable scientific evidence[2] of a causal association between Humira and lymphoma. (Note: Abbott has designated Dr. Feigal as one of its experts in this case.) Thus, it defeats Abbott's general causation *Daubert* motion as a matter of law. Because Abbott's specific causation argument is largely a derivative of its general causation argument, this too should defeat Abbott's entire motion.[3]

By way of explanation, Dr. Feigal was commenting on the significance of the 2006 amendments to the FDA labeling regulations, which now provide that potential adverse side effects can only be described in the warnings section of a drug label if there is "reasonable evidence of a **causal association** with a drug." 21 CFR § 201.57(c)(6). Prior to 2006, the warnings and precautions sections of drug labels listed side effects that were "temporally" related or associated,

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[1] Exhibit A at 1856:18-1857:11; 1859:5-1859:20.

[2] When asked if the regulations required "[s]ome reasonable scientific evidence of a causal association" Dr. Feigal responded, "Yeah.· They leave out scientific in the regs, but that's what they mean." *Id*.

[3] As she has done in all companion briefing, Plaintiff expressly incorporates all arguments, authorities, and exhibits in all the related briefing being filed concurrently with this Response, to include the Opposition to Abbott's Motion for Summary Judgment on Causation.

but without any further indication that there was a reasonable scientific basis to suspect an actual causal connection. The FDA was concerned that this resulted in over-warning. To remedy that concern, it inserted the requirement that there be "reasonable evidence" of a "causal association."

The FDA's GUIDANCE FOR INDUSTRY on the labeling requirements imposed by the 2006 amendments makes it clear that, in deciding whether there is reasonable scientific evidence of a causal association, the drug manufacturer and the FDA should both be looking at the same kinds of scientific factors that courts normally consider under *Daubert*. Exhibit B, FDA GUIDANCE FOR INDUSTRY: **Warnings and Precautions . . . Content and Format** (October 2011).[4]

In a recent opinion, a sister federal district court in Florida held that there was "nothing to meaningfully distinguish 'causal association' [within the meaning of this very regulation] from medical causation." *Guenther v. Novartis Pharmaceuticals Corp.*, 6:08-CV-456-ORL-31, 2013 WL 1278089 (M.D. Fla. Mar. 28, 2013). If that is true – as the pharmaceutical defendant itself argued in that case – then it follows, *ipso facto*, that a drug company's decision to list a side effect under the warnings or precautions section, in accord with this minimum safety standard regulatory requirement, is sufficient "reasonable scientific evidence" to defeat a causation *Daubert* motion.[5]

Dr. Feigal's concession about lymphoma is based on the fact that there is a "warning," in the warnings section, about it. *See e.g.*, Abbott's live Answer [Doc. 116] at 2-4. For it to be there, there must be "reliable scientific evidence" to back up a "causal association."

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[4] "Some factors to consider in assessing whether there is reasonable evidence of a causal relationship include: (1) the frequency of the reporting; . . . (3) evidence of a dose response relationship; (4) the extent to which the adverse event is consistent with the pharmacology of the drug [also called "biologic plausibility"] . . . (6) existence of dechallenge and rechallenge experience; and (7) whether the adverse event is known to be caused by related drugs." *Id*. at 3.

[5] In another recent *Daubert* opinion, a district court held that an FDA mandated warning, under this amended verbiage in 21 CFR §201.57 is one piece of evidence that the court can legitimately consider to support its decision denying the drug company's general causation *Daubert* motion. *In re Chantix (Varenicline) Products Liab. Litig.*, 889 F. Supp. 2d 1272, 1293-94 & n.22 (N.D. Ala. 2012).

Interestingly, Dr. Feigal's testimony from *Tietz* (which the Plaintiff won),[6] is in accord with the opinions of both of Plaintiff's experts in this case: her general causation and rheumatology expert, Dr. M. Eric Gershwin, and her specific causation/oncology expert, Dr. Dean McCracken.

Abbott simply cannot have it both ways. On one hand, they attempt to trumpet the purported "adequacy" of the warning information contained it their Humira package insert, and on the other, they move to exclude all of Plaintiff's scientific experts on the completely inconsistent notion that there is no reasonable scientific evidence that Humira can cause lymphoma. Because there is reliable, relevant, and reasonable scientific evidence of a causal association between Humira and lymphoma, Abbott's motion should be denied in all respects.

Overview

To defend claims that its blockbuster "tumor necrosis factor" medication HUMIRA caused Gayathri Murthy to develop cancer, Abbott invokes the *Daubert* line of cases and argues, mainly, that plaintiff's two experts are using unreliable methodologies and/or basing their testimony on flawed or incomplete scientific evidence. It makes this argument, largely predicated on a scientific discourse regarding epidemiology and "statistical significance" *even though* its own experts in this or other cases validate Plaintiff's experts' methodologies, *even though* statistical significance can normally not be found with regard to rare side effects, and *even though* the United States Supreme Court has recently opined that a lack of statistically significant data does not mean that medical experts have no reliable basis for inferring a causal link between a drug and adverse events.[7]

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[6] The *Tietz* jury ultimately found in favor of the Plaintiff and held Abbott to be liable for failing to warn about the risk of Humira induced unrecognized histoplasmosis despite a "double black-box" warning about infections. The court entered judgment in plaintiff's favor the same day, Exhibit C (*Tietz* Judgment).

[7] *Matrixx Initiatives, Inc. v. Siracusano,* —— U.S. ——, ——, 131 S.Ct. 1309, 1319, 179 L.Ed.2d 398 (2011). Although *Matrixx* was a securities case, recent pharmaceutical cases have cited it in support of their rejection of the "statistical significance" *shibboleth* in products liability cases. *E.g., In re Chantix (Varenicline) Products Liab. Litig*., 2:09-CV-2039-IPJ, 2012 WL 3871562 (N.D. Ala. Aug. 21, 2012) ; *In re Diet Drugs (Phentermine/Fenfluramine/ Dexfenfluramine) Products Liab. Litig*., MDL 1203, 2012 WL 3776692 (E.D. Pa. Aug.

To be clear, the pharmaceutical industry did **lose** *Daubert* itself, and, if one adopts Abbott's narrow, precise arguments for the very scientific orthodoxy that was rejected by the Supreme Court in that case, and if that results in a discretionary, exclusionary, dispositive ruling, it may wreak havoc with the entire system. Justice Breyer himself recognizes this in his Introduction to the 2011 REFERENCE MANUAL ON SCIENTIFIC EVIDENCE: THIRD EDITION:

> A decision wrongfully denying compensation in a toxic substance case, for example, cannot only deprive the plaintiff of warranted compensation but also discourage other similarly situated individuals from even trying to obtain compensation and encourage the continued use of a dangerous substance.

Id. at 4.[8] Justice Breyer elaborated that "the search is not a search for scientific precision. . . .The law must seek decisions that fall within the boundaries of scientifically sound knowledge.... science itself may be highly uncertain and controversial with respect to many of the matters that come before the courts." *Id*. And, more importantly, he reminds us all that the exercise of judicial discretion in must be made with an Article III sensitivity to the "basic human liberties . . . guaranteed by our Constitution's Seventh Amendment . . . the right to a trial by jury." *Id*. at 5. He adds:

> Any effort to bring better science into the courtroom must respect the jury's constitutionally specified role – even if doing so means that, from a scientific perspective, an incorrect result is sometimes produced.

Id.

Abbott's Illogical Incongruity

There is a fundamental incongruity in Abbott's litigation strategy. To advance the ball on

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30, 2012). This Court has also favorably cited to, and relied upon, *Matrixx* on multiple occasions for this very point. *See e.g., In re BP p.l.c. Sec. Litig*., 852 F. Supp. 2d 767, 788 (S.D. Tex. 2012)(Ellison, J.); *In re Anadarko Petroleum Corp. Class Action Litig*., 4:12-CV-0900, 2013 WL 3753972 (S.D. Tex. July 15, 2013)(Ellison, J.).

[8] Interestingly, however, that same judge wrote that "lymphoma caused by immunosuppressant drugs is well-understood," and suggested that the plaintiffs' experts' testimony would have been admissible if they had "compared the presentation of Andreas Perry's symptoms with those common in post-transplant lymphoma cases." *Perry v. Novartis Pharmaceuticals Corp.*, 564 F. Supp. 2d 452, 470 (E.D. Pa. 2008). This is, of course, precisely what Drs. Gershwin and McCracken did in their reports and methodology.

its learned intermediary defense, it argues that the relationship between HUMIRA and lymphoma was so well known and accepted by early 2005 when its clinical trial investigator Dr. Popovich prescribed it for Gayathri Murthy that the good doctor knew all about it. Abbott MSJ, Doc. 140 at 9/46. And, yet, to try to win the case on general and/or specific causation, it argues that there is really not enough scientific evidence linking HUMIRA to lymphoma to permit an inference of causation, and, ergo, that neither of the well credentialed and clinically experienced experts retained by Plaintiff's counsel in this case should be allowed to testify.

The "Science" Concerning Plaintiff's General Causation Opinions

Although their written reports do not use this matrix for analysis, the depositions of both sides' experts in this case, like *Calisi*,[9] reflect that they all utilize an analytical framework that focuses on nine separate factors or criteria that were first utilized by the United States Surgeon General in 1964 to assess the relationship between smoking and lung cancer and subsequently appropriated in 1965 by the Father of Modern Epidemiology, Sir Austin Bradford-Hill. REFERENCE MANUAL ON SCIENTIFIC EVIDENCE: THIRD EDITION, *Reference Guide on Epidemiology*, Section V at pp. 375-76 (National Academies Press, 2011)[hereinafter either "REFERENCE MANUAL" or "*Reference Guide*" as appropriate].[10] The use of these factors is "generally accepted" within the

[9] The *Calisi* case also involves allegations of Humira-induced lymphoma. Because of the similarity of plaintiff's allegations and expert proof, and Abbott's challenges to same, we have decided that, rather than cut and paste, we will simply attach the entire Statement of Undisputed Material Facts from *Calisi* as Exhibit D to this Motion [hereinafter "Calisi SUMFs"] and refer to it as necessary.

[10] The REFERENCE MANUAL has a number of different *Reference Guides* that provide an important resource for the Court. They include, not only the *Reference Guide on Epidemiology*, but one on statistics, another on "toxicity" and a third on "medical testimony."

There are nine of these so-called "Bradford-Hill" factors: (1) temporal relationship; (2) strength of the association; (3) dose-response relationship; (4) replication of the findings; (5) biologic plausibility (coherence with existing knowledge); (6) consideration of alternative explanations; (7) cessation of exposure [often described as "dechallenge" or "rechallenge"]; (8) specificity of the association; and (9) consistency with other knowledge. *See In re Neurontin Mktg., Sales Practices, & Products Liab. Litig.*, 612 F. Supp. 2d 116, 132 (D. Mass. 2009)(Recognizing, discussing, and applying Bradford Hill criteria in *Daubert* inquiry.). "These factors are viewed as guidelines, and it is acknowledged that each factor need not be fulfilled in order for a researcher to proclaim

meaning of *Daubert* and its progeny.[11] Moreover, as noted in the opening pages of this Brief, the FDA has "guided" Abbott and other manufacturers into using the same kinds of factors in making the decision as to whether there is sufficiently reasonable "scientific" evidence of a "causal association," within the meaning of 21 CFR §201.57, to warrant listing the adverse event as a side effect in the warnings section of the label.

It is a rare case in which all nine criteria will come into play. Indeed, as Bradford-Hill himself acknowledged, "none of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*." A. Bradford-Hill, *The Environment and Disease: Association or Causation?*, 58 Proc. Royal Soc'y Med. 295 (1965), quoted in *Reference Manual* at p. 376n.113. But the **majority** of these factors are present in this case, and militate in favor of the inference that Plaintiff's experts make. This is important because Abbott makes it sound like the only one of the nine that Dr. Eric Gershwin considered was biologic plausibility.

It is important to establish this nine-point framework early in this Memorandum, because Abbott's own 30(b)(6) witness acknowledge that most of them are present in this case. Dr. John Medich, Abbott's Rule 30(b)(6) designee on clinical trials, acknowledged that there were a number of cases, in Abbott's own clinical trials of HUMIRA and reported with other TNF agents, that were "temporally related." Exhibit D at ¶¶ 31-32. Of more significance, however, is his admission, and that of his Abbott colleague Dr. Aileen Pangan, that the relationship between HUMIRA and lymphoma was "biologically plausible." *Id.* at ¶¶ 26-27. Biologic plausibility is, according to the

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causation." *Id.*

[11] This Court's published opinions do not cite the *Reference Guide*. However, it has cited a similar federal manual as authority for rejecting a *Daubert* challenge to survey evidence. *Shell Trademark Mgmt. B.V. v. Warren Unilube, Inc.*, 765 F. Supp. 2d 884, 889 (S.D. Tex. 2011).

REFERENCE MANUAL's separate *Reference Guide on Medical Testimony*, the very first step of the "traditional scientific foundation" that supports a medical expert's opinion on causation. *Id*. at 741. Two Abbott executives testify that it is biologically plausible for Humira to cause lymphoma; but Abbott's lawyers brand Dr. Gershwin's discussion of the same biological pathway as "new and untested." There is a word to describe this phenomenon. Chutzpah!

Although numerous opinions by this Court indicate that a party does not have to have the most highly credentialed expert, in this case, Dr. Gershwin would most certainly fit that bill. Dr. Eric Gershwin, Distinguished Professor of Medicine at the University of California at Davis is very rare in that he is triple board certified in immunology, rheumatology and internal medicine. He also has a list of Peer-reviewed publications that looks like the phone book for a mid-sized American city. Exhibit F at 31-138 (Expert Report of Dr. Eric Gershwin). There is no expert in America who knows more about Humira and the other drugs in its biologic class than Dr. Gershwin. His extensive report highlights the biologic plausibility component and explains just why it is that Abbott's in-house experts were correct in conceding that the relationship between Humira and lymphoma is, indeed, biologically plausible. *See, e.g.*, *Id.* at 11/21.

Significantly, Abbott labels him as having been retained "exclusively for plaintiffs in pharmaceutical and medical device cases" in an effort to make him appear impartial and/or disreputable. This is disingenuous at best. For Dr. Gershwin specifically discussed with Abbott's counsel his testimony on behalf of asbestos manufacturers/defendants that asbestos exposure *does not* cause lymphoma. Exhibit G at 122:1-25 (Deposition of Dr. Eric Gershwin). He has so testified on multiple occasions, has done so within the last year, and is still testifying on behalf of asbestos defendants to this day. *Id.*

It is equally misleading for Abbott to suggest that Dr. Gershwin did not focus on the other

Bradford Hill factors or that his opinions relate solely to "theoretical mechanisms," untested or otherwise. Page 16/21 of his report describes a "key study" with clear positive dechallenge evidence. On the same page, he discusses the "broad immunological characteristics of anti-TNF-agents." That same page references other data that "reflect an increased risk of lymphoma." Dr. Gershwin is accused of ignoring the epidemiological data. Yet, his report clearly states that "there is clear epidemiological and scientific data that anti-TNF agents in general, and Humira in particular, cause an increase in the risk of developing lymphoma beyond the anti-inflammatory process itself." Report at 21. He also clearly detailed his methodology in his deposition as he goes through the various Bradford-Hill criteria and discusses each point he considered and the evidence that supports it. Exhibit H at 458:5-466:18 (Deposition of Dr. Eric Gershwin in *Calisi*).

Even more irksome is Abbott's litigation tactic of branding Dr. Gershwin's explanation that, by suppressing the immune system, the drug HUMIRA indirectly puts the human body at risk for lymphoma as a "new and untested theory." Abbott makes it sound very unscientific. And, yet, this very same, "biologically plausible" mechanism was recognized by Abbott upon Humira's launch in 2002, incorporated into the "Immune System" portion of the HUMIRA label, and quoted again in the following excerpt from Abbott's live Answer in this case:

> **5.11 Immunosuppression**
>
> The possibility exists for TNF blocking agents, including HUMIRA, to affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses.

Dkt. # 116 at 3/43 quoting HUMIRA label. Again, under the express wording of 21 CFR §201.57, as amended in 2006, Abbott could not put this language into the precautions section of its Humira label unless *it* believed that there is reasonable scientific evidence of a "causal association." Indeed, one of the principal cases cited by Abbott specifically makes the point that "lymphoma caused by

immunosuppressant drugs is well-understood" in medicine. *Perry,* 564 F. Supp. 2d at 470.[12]

It is also worth pointing out the tortured and incomplete deposition citations that Abbott has provided to this Court regarding the data Dr. Gershwin reviewed and considered. For example, Abbott boldly tells the Court that Dr. Gershwin refused to "even 'consider'" any epidemiologic evidence. This is, frankly, nonsense. The out-of-context answers that Abbott cites where provided in response to questions about whether a single article was the "largest meta-analysis" to date. Exhibit G at 164-165. To which Dr. Gershwin responded that while he is fully qualified to read and interpret epidemiologic papers, *and had read them*, he wasn't prepared to answer whether there existed in the known universe a larger meta-analysis or "full length Peer-reviewed study" with the specificity being asked. *Id*.[13] Additionally, he specifically cited in deposition Peer-reviewed publications with statistically significant elevated risks[14] as well as an animal study that demonstrated a 40% incidence of lymphoma in mice that had TNF dysregulation.[15]

Equally telling are admissions by Abbott senior executives acknowledging there have been lymphoma cases in their clinical trials that their own clinical investigators have determined are

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[12] In fact, to further highlight the incongruity between Abbott's litigation position and its scientific researchers, Dr. Gershwin specifically cited and relied upon testimony from Abbott's VP, John Medich, who testified that the immunosuppresion of Humira is what can increase the risk of malignancy with Humira. Exhibit F at 6.

[13] The other quotes concern the same type of questioning that had nothing to do with his opinions, but rather, whether he explored and analyzed "all of the epidemiology studies on lymphoma and anti-TNF's." Exhibit H at 452-453. Dr. Gershwin made it clear he is not an epidemiologist and did not spend his time compiling a detailed epidemiological canvassing of the literature *vis-à-vis* Humira and lymphoma, nor was he asked to render any opinions about general epidemiology on this issue. Further, it is unfair to say he did not consider epidemiology. A simple purview of the 113 references in his report belie Abbott's mischaracterizations of his testimony where reference after reference concern TNF inhibitors, malignancy, and risk. Exhibit F at 22-30.

[14] *See e.g.,* Exhibit H at 204:1-14. Here, Dr. Gershwin references, Mariette et al., *Lymphoma in Patients with Anti-TNF: Results of the Three Year Prospective French RATIO Registry*, 69 Ann. Rheum. Dis. 400, 404 (2010) (Finding odds ration of lymphoma after last using Humira or Remicade of 6.68 (1.90 to 23.54, p=.003); authors state that "[s]ome lymphomas associated with immunosuppression may occur and the risk of lymphoma is higher with monoclonal antibody therapy [Humira] than with soluble receptor therapy." Exhibit I at 400. This paper is also cited in his report. Exhibit F at 29, reference 94.

[15] Exhibit H at 256:17-25. The importance of the mouse study should not be underestimated. For the mouse is the model of human immunology "throughout the world." *Id*. at 164:20-165:10.

"probably related" to lymphoma. Exhibit D at ¶ 31. They also admit that it is quite possible that Humira causes lymphoma in patients through immunosuppression. *Id.* at. ¶29. And that there is a reasonable association between Humira and lymphoma. *Id.* at ¶28. Moreover, for an Abbott clinical trial investigator to find the relationship between Humira and lymphoma probably related, they would have to conclude that the lymphoma "followed a reasonable temporal sequence from administration of the study drug and could not reasonably be explained by the known characteristics of the patient's clinical state or concomitant therapy." *Id*. at 32.

More recently, *Abbott's Senior Medical Adviser*, in an internal email discussing an how to mitigate the fall-out surrounding an anticipated publication concerning a Humira patient who suffered a malignancy unambiguously stated that "the case clearly demonstrates a link between adalimumab[16] and this tumour." Exhibit J at 1 (Dhillon Email dated 12/20/07)(FILED UNDER SEAL ["FUS"].

In light of the above, the Court should deny Abbott's Motion and tell its counsel to rely on "'vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof."[17]

Argument and Authorities

I. THE *DAUBERT* FRAMEWORK.

This Court is, of course, intimately familiar with the *Daubert* line of cases and of its obligations and the Jury's prerogatives under the Seventh Amendment. The Court is well aware that the *Daubert* gatekeeping inquiry "is flexible and can adapt to the particular circumstances underlying

[16] Adalimumab is the generic name for Humira.

[17] *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 596 (1993). Needless to say, Plaintiff does not agree that the testimony of any of her experts is "shaky." However, the point of the quote from *Daubert* is that decisions regarding the *credibility* of expert witnesses must necessarily be made by the only one that is constitutionally empowered to do so, *i.e.,* the Jury.

the testimony at issue." *Hixson v. Houston Indep. Sch. Dist.*, 4:09-CV-3949, 2011 WL 3648104 (S.D. Tex. Aug. 17, 2011) reconsideration denied, 4:09-CV-3949, 2011 WL 4860004 (S.D. Tex. Oct. 13, 2011), citing *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 150–51 (1999). So, too, is it aware that, the nonmovant "need not show that the expert's findings and conclusions are correct." *Id*.

Finally, this Court's prior opinions indicate that it is acutely aware of the fact that, under *Kumho* in particular, an expert's opinion can be based on his/her experience, even in the absence of Peer-reviewed publication support...." *Black v. Toys R US-Delaware, Inc.,* 4:08-CV-3315, 2010 WL 4702344 (S.D. Tex. Nov. 10, 2010), citing *Pipitone v. Biomatrix, Inc.*, 288 F.3d 239, 246 (5th Cir. 2002). The touchstone, of course, is the "intellectual rigor" inquiry of *Kumho*. Again, plaintiff's experts meet and exceed that standard and utilize, in part, their extensive clinical experience.

Because of this Court's familiarity with the *Daubert-Kumho* line, there is no need to belabor the basic principles of the law at any great length. There are, however, two procedural anomalies that are worth mentioning. The first is the disparity between Rule 56 FED. R. CIV. P. and Rule 104, FED. R. EVID. Under the former, only evidence that is "admissible" constitutes proper summary judgment proof. On the other hand, Rule 104 provides that in making threshold decisions regarding admissibility under *Daubert* and its progeny, the Court is not bound to this standard. Thus, a dispositive ruling in favor of a party who has proffered inadmissible evidence is problematic.

The other anomaly is in the order of briefing and argument. The right to open and close is given to the party that bears the burden of proof as a fundamental tenet of due process. And there is no question but that, under *Daubert*, the proponent of expert testimony bears the burden of proof. Therefore, there is something incongruous about permitting Abbott first and last word.

In addition to the procedural anomalies noted above, there is, of course, also a due process anomaly in the discretionary standard of review. Pharmaceutical *Daubert* motions are ordinarily

dispositive in nature and therefore frequently coupled with a motion for summary judgment. The standard of review for the latter is de novo; the standard of review for a *Daubert* exclusionary ruling is discretionary. *See e.g., Mike Hooks Dredging Co., Inc. v. Marquette Transp. Gulf-Inland, L.L.C.,* 716 F.3d 886, 894 (5th Cir. 2013)(affirming discretionary decision to admit testimony of expert based on his experience). *Roman v. W. Mfg., Inc.,* 691 F.3d 686, 692 (5th Cir. 2012).[18]

Each of the cases in the *Daubert-Joiner-Kumho* triumvirate establish a different, but important point of law. First, with regard to *Daubert* itself,[19] it is important to begin from an understanding that the pharmaceutical industry *lost* the case. Both Merrell Dow and its pharmaceutical amici argued strenuously in the Supreme Court for adoption of the *Frye* standard of "generally accepted" orthodoxy. Obviously, if that were the law, then the industry's very widespread control of clinical trials and academic medicine could result in exclusion of countervailing expert opinions in almost all products liability pharmaceutical cases.[20] But the Supreme Court rejected the industry's approach, choosing instead, to control the "gates" of expert opinion testimony admissibility by focusing on four, non-exclusive criteria: "(1) whether the theory or technique

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[18] The discretionary standard of appellate review can be problematical for plaintiffs however, as the recent 2:1 Fifth Circuit case of *Johnson v. Arkema, Inc.*, 685 F.3d 452 (5th Cir. 2012) illustrates. Judge Reavley's opinion concurring in the reversal of the summary judgment lamented that the Court's ruling denied "the trier of fact the testimony of these highly qualified expert witnesses" and pointed out that the majority of the court had set up a standard for admissibility that simply could not be met by anyone. *Id*. at 473. Judge Gray of this Court recently distinguished *Johnson* in the course of an opinion denying both a motion to exclude and a motion for summary judgment by a pharmaceutical defendant. *Silverman v. Watson Pharmaceuticals, Inc.*, CIV.A. H-10-1952, 2013 WL 1645771 (S.D. Tex. Apr. 16, 2013).

[19] *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993).

[20] The dangers of such control is made clear by Abbott's persuasive and systematic "ghostwriting" of peer-reviewed literature and use of Key Opinion Leaders ("KOLs") to sway medical consensus. *See* Exhibit D at ¶¶ 3-17, 74. "Ghostwriting" is the Abbott employed practice of internally drafting favorable Humira literature that it asks highly recognized doctors which with it has a financial relationship to "author" for "peer-review." Abbott has a handful of KOLs it holds as "advocates" and "partners" under whose name it publishes favorable literature. This literature is then used in its marketing efforts and in its *Daubert* motions. Abbott's "ghostwriting" is discussed in the *Calisi* SUMFs. The New England Journal of Medicine has also addressed this troublesome practice. *See* Bodenheimer T, *Uneasy Alliance — Clinical Investigators and the Pharmaceutical Industry*, N Engl J Med 2000; 342:1539-1544. Exhibit K. There is simply insufficient space to further discuss herein.

applied can be tested, (2) whether the theory or technique has been subject to peer-review or publication, (3) the known or potential rate of error, and (4) whether it is accepted in the relevant discipline." *Id*. The general causation opinions of both experts in this case pass muster under all four criteria, although we address them in inverse order.[21]

Joiner[22] is important because it underscores the notion that these are *discretionary* decisions. The breadth of discretion accorded to trial judges is extremely significant. The *Kirby* case cited by Abbott provides an excellent example. There, with none of the judicial admissions, Peer-reviewed literature, adverse event data, Bradford Hill factors, and *Daubert* factors that are present in this case, the Fifth Circuit affirmed a trial judge's discretionary decision to exclude expert testimony in a lymphoma case. Yet, even in so doing, it uttered the following words of caution about the limitations of epidemiology and the dangers of judicial reactionism:

> We also understand that in epidemiology hardly any study is ever conclusive, and we do not suggest that an expert must back his or her opinion with published studies that unequivocally support his or her conclusions. ... Where an expert otherwise reliably utilizes scientific methods to reach a conclusion, lack of textual support may "go to the weight, not the admissibility" of the expert's testimony. . . . A contrary requirement "would effectively resurrect a *Frye*-like bright-line standard, not by requiring that a methodology be 'generally accepted,' but by excluding expert testimony not backed by published (and presumably peer-reviewed) studies."

Knight v. Kirby Inland Marine Inc., 482 F.3d 347, 354 (5th Cir. 2007)(citations omitted). *But see Kuhn v. Wyeth, Inc*., 686 F3d 618, 625-633 (8th Cir. 2012)(Abuse of discretion to exclude causation expert despite favorable epidemiological evidence for defendants because of limitations of clinical

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[21] First, Dr. Gershwin's use of the Bradford Hill factors is generally accepted. Exhibit D at ¶¶ 58-67. Second, the rates of error, or "*p*-values" in many of the studies upon which their opinions are partially based, are within scientific norms. *Id.* at ¶¶ 13, 15, 44-45, 59. Third, their opinions are based on peer-reviewed literature, including an article published in JAMA, and recently cited by the FDA as "new safety information," which found statistically significant risk ratios between biologics like HUMIRA and cancer. *Id*. Finally, although Abbott has certainly not devised a clinical trial to "test" the hypothesized relationship, the dechallenge evidence is a de facto mini-scientific experiment. *Id.* at ¶ 20.

[22] *General Electric Co. v. Joiner*, 522 U.S. 136 (1997).

trial data *vis-à-vis* rare side effects.).

In spite of the fact that *Daubert* motions have become *de rigeur* tactics for pharmaceutical companies, "a review of the case law after *Daubert* shows that the rejection of expert testimony is the exception rather than the rule. *Daubert* did not work a 'seachange over federal evidence law,' and 'the trial court's role as gatekeeper is not intended to serve as a replacement for the adversary system." Official Comments to 2000 Amendment to Rule 702, FED. R. EVID.

II. PLAINTIFF'S EXPERTS' GENERAL CAUSATION OPINIONS PASS *DAUBERT* MUSTER.

A. The General Causation Opinions are Based on Generally Accepted Scientific Principles. Not even Abbott can seriously argue either (a) that the Bradford Hill factors are not generally accepted, or (b) that Drs. Gershwin's and McCracken's opinions are not consistent with them. To the contrary, there is a wealth of scientific evidence that supports the general causation opinions of her experts. Temporal relationship. Biological plausibility. Dose response. Consistency. Peer-reviewed science with statistically significant risks of 2.0+.[23] Dechallenge. Animal studies/experiments. These "Bradford Hill" factors are the hallmarks of "general acceptance" and, thus, satisfy the first *Daubert* criterion.

B. Plaintiff's Experts Cite and Rely on Peer-Reviewed Data and Literature. The second, *i.e.,* "Peer-review" is also well satisfied. Dr. Gershwin's extensive report cites numerous Peer-reviewed journal articles – several authored by himself – to support his opinions in the case. Similarly, Dr. McCracken's report reflects that it, too, is based in part on the Peer-reviewed "scientific literature." Exhibit M at 22-38 (Expert Report of Dr. Dean McCracken). The cited

[23] Despite criticisms that he ignored epidemiology, Dr. Gershwin also reviewed an epidemiological report by epidmiologist Dr. David Goldsmith. Although Plaintiff chose not to formally designate him in this case, Dr. Gershwin reviewed this literature in formulating his opinions. *Id*. at 21. Dr. Goldsmith's report from *Calisi* is attached as Exhibit L hereto.

literature are not simply "anecdotal case reports," but rather scientific studies that have the traditional hallmarks of reliability, *i.e.,* "dechallenge . . dose response . . . increased risk of lymphoma from clinical trial data." *Id.* at 3. To the extent that the pertinent scientific evidence is available in the Peer-reviewed public domain[24], it has been considered and cited by both of Plaintiff's experts. He also extensively cites deposition testimony of Abbott scientists and Abbott internal documents. *Id.* at 2, 5-7, 11-12.

C. The "Theory" has been Tested. Obviously, no one would design and conduct a clinical trial to see if Humira actually causes cancer. But, the data from Abbott's clinical trials is damning. This is controlled, clinical data, and it shows an elevated risk of lymphoma for patients taking Humira versus that for the same patients from the same patient population who are not. Exhibit D at ¶¶ 34-35 (Admitting that there was a statistically significant increased risk of lymphoma found in Humira RA clinical trials before Humira went on the market.)[25] Also, the scientific literature cited by both Gershwin and McCracken that contains reports of "dechallenge" evidence[26] is, as the *Reference Guide* notes, a mini-scientific test or experiment of sorts. So, to the extent that there is information in this category, it has been considered and it supports the experts' opinions.

D. The Rates of Error are Within Scientific Norms. This *Daubert* factor really

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[24] There is, of course, considerable hubris in Abbott's focus on the Peer-reviewed component. The large majority of the most damning evidence – more than eight million pages of which were produced in this and related litigation – has been hidden from public scrutiny by reputable academicians by virtue of Abbott's lawyers' "CONFIDENTIAL". stamp. Much of it is now on file with this Court and with the *Calisi* court in Massachusetts.

[25] *See also* current label warning of 3-fold higher rates of lymphoma in Humira treated patients compared to the general population. http://www.rxabbvie.com/pdf/humira.pdf at 11. While the label goes on to say the rates are not directly comparable because of the increased risk from inflammation due to RA, the results are taken not just from RA clinical trials but across all data. Further, if the risk of lymphoma is tied to inflammation, and if Humira reduces the inflamation and is protective, then the rates should actually be reduced from what is expected. They are not. Dr. Gershwin makes this very point. Exhibit H at 361:22-362:6.

[26] Exhibit D at ¶20 (Brown, *et. al., Tumor Necrosis Factor Antagonist Therapy and Lymphoma Development: Twenty-Six Cases Reported to the Food and Drug Administration*, 46 Arthritis & Rheumatism 3151 (2002) (App. 41) is a peer-reviewed publication citing two cases of "dechallange": In 1 case (patient 17 in Table 1) the lymphoma was observed to shrink and necrose after the discontinuation of the TNF inhibitor.

focuses in on the "p-value" used for scientific publications. Because the literature cited by Plaintiff's experts is, by and large, Peer-reviewed, it has the customary, acceptable .05 rate of error.

III. THE *KUMHO* "INTELLECTUAL RIGOR" STANDARD IS MET AS WELL

When Rule 702 was amended, in 2000, there was some notion that it would enshrine the four *Daubert* criteria as essential factors for the admissibility of all expert testimony. But the Supreme Court refused to do so. Instead, it reiterated that "all of these factors remain relevant . . . yet no single factor is necessarily dispositive." Official Comments to 2000 Amendments. However, if there is a litmus test, it is the "intellectual rigor" standard of *Kumho*, reiterated in the comments to the 2000 amendments. *Black v. Toys R US-Delaware, Inc.*, 4:08-CV-3315, 2010 WL 4702344 (S.D. Tex. Nov. 10, 2010).

Both Dr. Gershwin and Dr. McCracken base their opinions, not only on publications and epidemiology and the documents and testimony from Abbott itself, but also on their extensive clinical experience. *Kumho* teaches that a person's experience can be adequate, in and of itself, to justify opinion evidence. *Kumho,* 526 U.S. at 152). This Court so held, with regard to the physician expert in *Toys R US, supra*. The REFERENCE MANUAL's *Reference Guide on Statistics* echoes this sentiment with regard to clinical experience: "In medicine, evidence from clinical practice can be the starting point for discovery of cause-and-effect relationships." *Id*. at 217n.

A. Dr. Eric Gershwin is the Epitome of "Intellectual Rigor". In this case, as in *Calisi*, Abbott tries to paint a false picture of Dr. Eric Gershwin. As a distinguished, widely published Chief of Rheumatology and Immunology at a prestigious medical institution, Dr. Eric Gershwin is uniquely qualified to help the Court's Jury understand HUMIRA and its impacts, both beneficial and adverse, on the human body. He has encyclopedic knowledge, experience and education in both rheumatology and immunology, two fields of science/medicine that are key in this

case. Exhibit F at 31. He also has the ability to convey that knowledge in understandable ways to lay people. Abbott leveled no exclusionary challenge whatsoever to Dr. Gershwin's testimony in the *Tietz* trial. His testimony obviously helped the jury reach a verdict.

Nonetheless, because it has no basis to attack either his credentials, or the foundation of his opinions (with the exception of its "statistical significance" arguments), in this case as in *Calisi*, Abbott takes the tack of taking on the witness himself.

If the Court was only to read Abbott's Motion to Exclude Dr. Gershwin, it would leave with the impression that he is some kind of hack who has been continuously excluded under Rule 702. In fact, the Chief of Immunology and Rheumatology for UC Davis looks nothing like the picture Abbott attempts to paint. Dr. Gershwin has testified in trial between 50 and 100 times during the course of his 40-year career. Exhibit H at 8:4-8:10. And in those 50-100 instances, Abbott can find only four cases with cherry picked commentary where the court has been critical of Dr. Gershwin or limited *portions* of his opinion testimony.

It begins by citing two cases that took place in front of Article I courts related to the vaccine compensation program.[27] These courts do not apply Rule 702, *Daubert*, or *Kumho* in the same way as Article III judges and do not have the constitutional constraints of which Justice Breyer spoke in the foreword to the REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, *supra*. Second, with regard to the Latex glove litigation where Dr. Gershwin offered six opinions, the court limited only one of his six opinions, and he was not "precluded from testifying to the foundations and reasons given for this [sixth] opinion." *In re Latex Gloves Products Liab. Litig.*, 1148, 2002 WL 992037 (E.D. Pa. May 10, 2002). Finally, in the breast implant litigation that took place more than 15 years ago, the court's technical advisor believed that Dr. Gershwin "made too great a leap from the underlying data to his

[27] *Barber v. Sec'y of Health & Human Services*, 99-434V, 2008 WL 4145653 (Fed. Cl. Aug. 21, 2008); *Gard-Valdez v. Sec'y of Health & Human Services*, 95-686V, 1998 WL 458369 (Fed. Cl. July 20, 1998).

conclusions" *Hall v. Baxter Healthcare Corp*., 947 F. Supp. 1387, 1411 (D. Or. 1996). However, in this case, given his clear reliance on the generally accepted Bradford Hill criteria, as well as Abbott's admission that support his analysis, he has clearly employed a reliable methodology that involves no "leap" at all. Exhibit D at ¶¶ 58-67.[28]

Abbott likewise attempts to diminish Dr. Gershwin's opinions in this case by citing a 2006 article he coauthored wherein the authors stated that a causal link between TNF-blockers and lymphoma could not be found from the publicly available information at that time. Kong et al., *Potential Adverse Events with Biologic Response Modifiers*, 5 Autoimmunity Reviews 471 (2006), discussed at Abbott's Memo at 18-20. The obvious retort to this argument is that Dr. Gershwin did not have access to the large amount of **CONFIDENTIAL** stamped documents from Abbott that he both listed in, and relied upon, in creating his expert report in this case, including 30(b)6 deposition testimony of Abbott employees, internal Abbott documents, and confidential emails. Exhibit F at 1-3.

Furthermore, when confronted with this publication in his *Calisi* deposition, Dr. Gershwin explained by stating that (1) the lymphoma portion "wasn't the major part of the [2006] article," (2) he "did not look at the lymphoma issue "in depth," (3) he relied "mostly on the label" at the time the article was written, (4) there "was significant [new] data published in 2006 and since," and (5) there was important data published in 2004 that he wasn't aware of at the time. Exhibit H at 59:1-59:3; 93:4-93:11; 97:8-97:16. Additionally, he noted that this was minor point of his paper and did not

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[28] Q: So, Dr. Gershwin, I -- could you spend some time talking about the methodology you used in this case to determine that Humira can cause lymphoma?

A: I can if I can find my notes. So I used Bradford Hill criteria of causality.

Id. "I would only testify if I was certain I could fulfill Bradford Hill criteria with appropriate methodology to address that issue....I left no stone unturned particularly with respect to methodology in Bradford Hill...the basis of my opinions contains additional material that will fulfill Bradford Hill criteria and reflect the methodology I used, and in addition will discuss experimental evidence, which is Number 8 of the Bradford Hill criteria." *Id*.

receive the depth that the subject deserves. *Id*. at 94:24-95:10. Bottom line: the 2006 article is fodder for cross examination, not exclusion.

Abbott also contended in their *Calisi* challenge to Dr. Gershwin that when Dr. Gershwin was confronted with epidemiological evidence related to HUMIRA and lymphoma he "folded" and acknowledged there was none. This is patently false. Dr. Gershwin, when laying out one of the nine Bradford Hill factors (strength of association) he analyzed in this case, included the epidemiological evidence presented to him by Abbott's counsel:

> Firstly, the association we're looking for is lymphoma. Indeed. The trend in all of these studies has been towards an increased incidence of lymphoma. There were wide confidence intervals within these studies. This is an uncommon event and likely indicates that there will be a small group of people with a genetic predisposition. That's why the confidence interval is wide. And that's why it's been difficult within these studies to come up with a relative risk of greater than two.

Id. at 459:22-460:6. In fact, the "trend" is that almost all of the epi studies show a positive risk association[29] and the upper limits of the confidence intervals demonstrate that the real risk could be literally off the charts.

These studies that Dr. Gershwin refers to are cited in a chart on page 26 of Exhibit N. Solomon et al., *Observational Studies on the Risk of Cancer Associated with Tumor Necrosis Factor Inhibitors in Rheumatoid Arthritis: A Review of Their Methodologies and Results*, 64 Arthritis & Rheumatism 21, 26 (2012). Not one study on that chart has a point estimate for lymphoma or hematological cancers below 1.00, with the vast majority having point estimates above 1.00. *Id*. Therefore, the trend, as Dr. Gershwin states, is indeed toward an increased risk of lymphoma.[30] *See*

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[29] Which Abbott 30(b)(6) witnesses admit. Exhibit D at ¶ 28.

[30] The authors state that "[m]ost studies demonstrated a numerically increased risk for lymphoproliferative cancers." *Id.* at 27. The authors further state that "[s]everal consistent patterns emerge from these data. The SIR for all cancers among patients receiving TNF inhibitors in general did not increase. However, the SIRs for lymphoma and hematologic malignancies are increased." *Id.* at 29. Also, this study was funded entirely by Abbott. *Id.* at 21. What the article does not mention is that it was coauthored by an Abbott "True Partner" KOL. *See* Exhibit D at ¶ 13. Abbott does not view Dr. Kavanaugh as an independent. *Id.*

also the most recent meta-analysis published in JAMA, which contains a point estimate of risk of 2.1. Exhibit D at ¶ 17.

Next Abbott would have the Court believe that Dr. Gershwin's opinions were based on biological plausibility alone, and more specifically on animal studies. This too is patently false. Dr. Gershwin found support for all nine Bradford Hill factors he analyzed in this case. *Id.* at ¶¶ 58-67. The animal studies Abbott focuses on, while important, were used to substantiate three Bradford Hill factors (theoretical plausibility, specificity in cause, and experimental evidence). *Id.* So, while the animal studies were an important component, they were only one component he considered along with epidemiological studies, dose response evidence, dechallenge evidence, and multiple analogous examples where immunosuppression caused lymphoma. *Id.* There is certainly nothing wrong with using animal studies. Indeed, the *Reference Guide* itself points out that "[a]nimal studies have a number of advantages. . . . Animal studies often provide useful information about pathological mechanisms and play a complementary role to epidemiology by assisting researchers in framing hypotheses and in developing study designs for epidemiologic studies." *Id.* at 563.

Finally, it should be noted that Dr. Gershwin's general causation opinion has been corroborated by the other scientific evidence, chronicled at length in Exhibit D and Brief in Response to Abbott's Motion for Summary Judgment. This includes critical admissions in Abbott's pleadings, its documents, the testimony of its witnesses, and the causality assessments[31] of its own clinical trial investigators.

B. Dr. Dean McCracken's "Intellectual Rigor." Interestingly, Abbott does not attack either Dr. McCracken's credentials or his "rigor." What they do instead is try to marginalize his

[31] Abbott will try to downplay the significance of its own pharmacovigilance activities and internal causality assessments. Nonetheless, as the recent opinion in *Newman v. McNeil Consumer Healthcare*, 10-CV-01541, 2012 WL 39793 (N.D. Ill. Jan. 9, 2012), illustrates, this kind of evidence is significant, not only to the FDA, but also to gatekeeping courts.

experience by portraying him as a man who is an expert at *treating* a condition, but who is blithely ignorant about the things that actually cause the condition he treats.

As his report reflects, Dr. McCracken bases his opinions, *inter alia*, on clinical experience as an oncologist "for greater than 40 years" and employed that experience in arriving at his conclusions in this case. Exhibit O at 278:20-279:6 (Deposition of Dr. Dean McCracken).[32] Contrary to Abbott's argument, that Dr. McCracken simply adopted Dr. Gershwin's opinions about the immunological pathway between Humira and cancer, Dr. McCracken himself elaborates that "my experience as an oncologist makes me keenly aware of the immunosuppressive effects of Humira. Immunosuppression is a profound risk factor for lymphoma." Exhibit M at 1-2. He details his analysis of this case, explaining that he used the well recognized, medical standard methodology of "differential diagnosis." *Id.* at 2-5.[33] It explains that he made a list of all potential risk factors and considered, and ruled out, all of them as the total explanation for Gayathri Murthy's cancer. *Id.*

Abbott's specific criticisms of Dr. McCracken are as misleading as those it lodged against Dr. Gershwin. Dr. McCracken makes clear that while statistics and significance are important considerations, from a clinical standpoint they are a simply a "number." Exhibit O at 139:25-142:4.[34] Despite's Abbott's questioning and assertions, Dr. McCracken made clear that in his experience, statistical significance is not "all or nothing" or "yes or no" with respect to the practice

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[32] Dr. McCracken has treated hundreds of lymphoma patients during his career. *Id*. at 229:10-11.

[33] Therein noting that he employed a differential diagnosis and considered Mrs. Murthy's age, rheumatoid arthritis, immunosuppresion, exposure to other carcinogens, and general medical history. He further explains, "[i]n attempting to rule in or rule out these various factors, I have also reviewed and relied upon scientific literature related to the relationship between TNF-blockers and malignancies/lymphoma as well as various Abbott documents and depositions of Abbott employees and experts." *Id.*

[34] Specifically, he stated that once you have statistical significance, "it becomes very hard to dispute" causation. *Id*. Thus, the *Bongartz* study, upon which Dr. McCracken specifically relied, page 5 of Exhibit M, makes it "very hard" for Abbott to dispute causation. Bongartz et al. (2006) *Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infection and malignancies: Systemic review and meta-analysis of rare harmful effects in randomized clinical trials*. Journal of the American Medical Association 295: 2275-2285 (2006) finding statistically significant odds ration for all malignancies in TNF treated patients (3.3, 95% CI,1.2-9.1).

of real world medicine. *Id*. He offered the following example of his clinical experience to keep us grounded in reality:

> "I think there are a lot of studies, in my opinion, that have shown that the statistical significance is– is good. It's a standard that most people apply. But there are a lot of patients that are – that have treatments with nonstatistically [sic] significance. Depends on how they – the statistics are created by the statistician. They're very – variety of ways to do statistics, but there are many cancer patients alive and well today on treatments that were never statistically significant in their disease...But I have patients that are treated with drugs that aren't statistically significant by the standard for the patient; that have their pain relieved, they have their symptoms relieved, they have their tumors stop growing, and they have many, many positive benefits. So statistics are great, but they're not all encompassing."

Id.

Additionally, although he may primarily treat the disease, Dr. McCracken, as part of his clinical practice routinely assists patients with trying to determine what caused their lymphoma/malignancy. *Id.* at 112:9-18 (II). To wordsmith and say that he has never been called upon to determine if a TNF-inhibitor caused a patients lymphoma is disingenuous. As part of his practice he discusses with cancer patients their particular risk factors and things than should be considered towards what may have caused their cancer. *Id.* And while in many cases cancer is idiopathic, there are factors that distinctly increase the risk and play a known role in cancer development. *Id.* Thus, as part of this very discussion, and exactly like he did in this case, he uses a differential diagnosis to deduce what caused cancer in one of his patients. *Id*. at 280:15-281:12 (II).

Moreover, Dr. McCracken did more than simply adopt Dr. Gershwin report to arrive at his conclusions. He relied upon his clinical experience, statistically significant peer-reviewed literature,[35] Abbott 30(b)(6) admissions, and Abbott internal causality assessments documenting that patient

[35] *See* Exhibit M at 2-5. He also stated that he fully considered studies that showed no statistically significant results, but that "the totality of the evidence...plus my clinical experience and the well-known effects of immunosuppresion," drove him to his conclusions.

lymphomas were "probably" related to Humira. *Id.* at 275:14-276:19 (II). *See also* Exhibit M at 2-5. Further, he did not accept Dr. Gershwin's report without first applying his medical training and expertise to its contents. Exhibit P at 67:10-68:2 (Deposition of Dr. Dean McCracken).

Particularly compelling to him is the potency of the immunosuppressive effect of Humira. *Id.* at 70:22-71:18 (I).[36] That, in the absence of any other recognized risk factors in the Plaintiff, is what ultimately lead him to conclude that Humira caused or contributed to Mrs. Murthy's lymphoma. Exhibit M at 2. Specifically, Mrs. Murthy had no other risk factors for lymphoma. *Id.* Her RA was neither long standing nor severe,[37] and as such, the inflammatory process that Abbott trumpets as the true cause of lymphoma in RA patients is notably absent. *Id.* at 2-4.[38] She also had no evidence of any lymphoid process prior to Humira as documented by a fulsome medical record. *Id*. Thus, given the strong immunosuppresive effect of Humira, the literature, Abbott admissions/internal causality assessments, and current FDA warnings, Dr. McCracken was able to rule out the other likely causes of her lymphoma. *Id*.

Abbott's "rule out" arguments ignore a critical distinction in the law. Plaintiff does not have to prove that Humira was the sole cause of her cancer, only that it was **a** proximate or producing cause. Abbott argues, however, that, for her experts' testimony to be admissible, they must prove

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[36] The other medication that Plaintiff was taking, methotrexate, was a mild immunosuppressant according to Dr. McCracken. Exhibit O at 267:18-268:12. TNF-inhibitors like Humira are much "higher..more potent" inhibitors. *Id.* To say he did not rule this medication out is untrue.

[37] Abbott overstates so called admissions by Dr. McCracken that Plaintiff had an eight-fold increase in lymphoma risk due to her RA. The cited article, and the question itself, reflect that this risk was for patients with medium overall disease activity. Exhibit O at 100. Mrs. Murthy had neither long standing nor moderate RA according to Dr. McCracken and Dr. Gershwin.

[38] Abbott completes usurp the record when it says Dr. McCracken could not "rule out [the] possibility" of various contributing factors. With respect to *each* of these points, Dr. McCracken was asked whether he could "*completely*" rule out these items. Dr. McCracken made it clear in his deposition and report that "while he could not completely rule out a possible contribution from [RA]...given the short duration of Mrs. Murthy's RA I believe the immunocompromising effects of Humira to be the most likely cause of this relatively atypical and aggressive form of lymphoma. The immunosuppressive effects of Humira are profound." *Id.* We invite the Court to review the actual transcript to see how this important modifier was omitted from Abbott's brief.

that the "sole cause" is not something else. This is not the law. "Sole cause" is an affirmative defense. *See e.g., Buffalo Marine Servs. Inc. v. United States,* 663 F.3d 750, 759 (5th Cir. 2011). The truth is, as the *Cano* case cited by Abbott illustrates, an expert is only required to consider and **"quantify"** potential alternative causes, and to have a reasoned scientific basis for concluding that the Humira was the most "probable" significant cause. *Cano v. Everest Minerals Corp*., 362 F. Supp. 2d 814, 840 (W.D. Tex. 2005). This is precisely what Dr. McCracken did in his differential diagnosis analysis of the various potential risk factors, including "idiopathic."

More fundamentally, with respect to idiopathic disease, what's being left unsaid is that these "80 to 90 percent" of cases do not have the tremendous immunosuppressive effects of Humira at play or other obvious risk factors. Thus, unlike this case, when a patient is on Humira and develops lymphoma, then the physician is able to factor this into consideration in a differential diagnosis as to disease etiology.[39] While there is no laboratory test for distinguishing from lymphoma caused by anti-TNFs or other causes, that is a red-herring. The differential diagnosis is the methodology that provides the means by which medical professionals can examine an individual patient and rule in/out known causes. It is well accepted and widely practiced.

One of the things that Dr. McCracken notes in his specific causation opinion is that Mrs. Murthy had a "relatively atypical and aggressive *form* of lymphoma." This is an important distinction in this case (as in *Calisi*). Interestingly, the ability of medical doctors to differentiate between various types of lymphomas is one of the examples used in the following excerpt from the REFERENCE MANUAL ON SCIENTIFIC EVIDENCE: THIRD EDITION, *Reference Guide on Medical Testimony*, to explain how "advances in medical technologies" will cause the "practice of medicine"

[39] Exhibit O at 98:3-16 (Discussing that while most patients development of lymphoma is idiopathic, it varies between patients; some patients have been exposed to carcinogenic substances, have genetic predispositions or familial history that allow you to examine causation.).

to be "profoundly altered and redefined."

> For example, consider lymphoma, a blood cancer that used to be classified by appearance under the microscope as either Hodgkin's or non-Hodgkin's lymphoma. As science has evolved, it is now further classified by cellular markers that identify the underlying cancer cells as one of two cells that help with immunity (protecting the body from infection and cancer): T cells or B cells.

Id. at 740-41. As Dr. McCracken explained in his Rule 26 Report, Gayathri Murthy had a "diffuse large cell lymphoma." The aggressive nature of this particular type of lymphoma, coupled with the clear role of immune suppression in the development of same, and the dose response relationships and positive dechallenge evidence, were all compelling evidence that this was, indeed, a HUMIRA-*induced* **form** of lymphoma. He used the very same differential diagnosis he uses in his everyday medical practice. Exhibit O at 279:18-21. If the 2011 Federal REFERENCE MANUAL is to be believed, Dr. McCracken's opinions are admissible.

Conclusion

The following conclusion, written by this Court in its *Toys R US* opinion, applies with equal force [with a change of names and specialties] to the case at bar:

> The *Daubert* factors are not required in all situations and the present case is one such example. The Court is satisfied that Dr. [Gershwin and McCracken] has brought to "the courtroom the same level of intellectual rigor that characterizes the practice of an expert" in [rheumatology/immunology and oncology] by engaging in an in-depth analysis of the relevant medical and other records and applying standard diagnostic techniques of to arrive at his conclusions. In short, the potential shortcomings Defendants have identified in Dr. [Gershwin's and McCracken's] testimony go to its weight, not its admissibility. Indeed, "Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence."

Black v. Toys R US-Delaware, Inc., 4:08-CV-3315, 2010 WL 4702344 (S.D. Tex. Nov. 10, 2010)

Abbott's Motion to Exclude Causation Testimony under Federal Rule of Evidence 702 should be denied.

Respectfully submitted,

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Certificate of Service

I certify that on this 30th day of July, 2013, Plaintiff's Response in Opposition to Defendant's Motion to Exclude Causation Testimony has been electronically filed with the Clerk using the CM/ECF system, which will automatically send email notifications of such filing to the following attorneys of record:

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